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Recent Progress in the Treatment of Epithelial Ovarian Malignancy

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Improved surgical and chemotherapeutic management has ensured that more than half the patients with advanced ovarian cancer will be clinically free of disease shortly after treatment begins. Aggressive cytoreductive surgical treatment and combination cytotoxic chemotherapy have appreciably prolonged survival and have induced cures in some women with metastatic disease. An increasing number of women are being seen with small residual disease at second-look laparotomy, and intraperitoneal administration of chemotherapeutic and immunotherapeutic agents is being investigated for these patients. Specific immunotherapies, including monoclonal antibodies raised against patients' own tumor cells, are also being investigated. During the next five years we may see significant improvement in the cure rate for this disease.

OF ALL THE DISEASES unique to women, malignant disease of the ovary is a foremost cause of death in the United States. Over 11,400 women succumbed to ovarian cancer in 1981.[1] According to some estimates, this disease develops in 1 of every 70 women in the United States.[2]

Epidemiologic studies have failed to identify any consistent predisposing factors associated with the disease. The increased prevalence of ovarian cancer in single women, however, including nuns and nulliparous married women, suggests that incessant ovulation uninterrupted by pregnancy may be a predisposing factor.[3]

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Unfortunately, in more than 70 percent of cases, ovarian carcinoma has metastasized by the time it is diagnosed.[4] Diagnosis is usually suspected after detection of a pelvic or abdominal mass on clinical examination, and confirmed at exploratory laparotomy. This is because ovarian carcinoma tends to be asymptomatic until the disease is advanced, and no sensitive screening test is available to asymptomatic women.

Transcoelomic spread is the most common form of dissemination, with metastasis commonly occurring in the omentum, paracolic gutters and undersurface of the diaphragm. Lymphatic dissemination also occurs early in the course of the disease, with pelvic and periaortic lymph nodes frequently involved. With more advanced disease, lymphatic channels in the diaphragm become blocked, resulting in clinically evident ascites.

Metastasis via blood vessels rarely occurs, so most patients with advanced disease do not have spread outside the abdominal cavity.

Treatment

Chemotherapy

Chemotherapy has been the primary therapy for advanced ovarian malignancy. Whereas single alkylating agents were the treatment of choice for many years, multiagent combination chemotherapy is now becoming the standard treatment. Agents such as cisplatin, doxorubicin hydrochloride, cyclophosphamide, hexamethylmelamine and vinblastine sulfate have shown activity against these tumors. Recent reports indicate that response rates of about 70 percent to 80 percent may be expected in patients with stages III and IV disease. Approximately half of these patients will have complete clinical responses. Such patients have been reported to have actuarial survival rates of greater than 50 percent at three years.[5] More complete responses to chemotherapy have been seen in patients who have had optimal tumor cytoreduction before beginning their therapy.[5,6] In addition, it has been shown that combination chemotherapy is better than single alkylating agents only when used in patients who have undergone optimal cytoreductive surgical treatment.[5]

Surgical Procedures

Several studies have indicated the value of reducing the tumor burden at the start of chemotherapy.[6,7] When the size of the largest residual tumor at the beginning of chemotherapy is less than 1.5 to 2 cm, patients have been shown to have a longer median survival, independent of tumor grade. These reports have prompted many gynecologic oncologists to do an initial cytoreductive surgical procedure in a further attempt to prolong life and achieve a cure following multiagent chemotherapy.

Our approach has been to do cytoreductive operations in all cases with a primary diagnosis of ovarian cancer, and occasionally in cases with a primary diagnosis of recurrent or persistent disease. The operation typically consists of a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, resection of paracolic and peritoneal tumors, selective lymphadenectomy and occasionally bowel or lower urinary tract resection. In our experience, optimal surgical cytoreduction (that is, the largest residual mass being 1.5 cm in diameter) can be accomplished in about two thirds of patients with advanced disease (stages III and IV).[8]

Our results indicate that the amount of residual disease following surgical intervention, the presence of clinical ascites and the diameter of the largest metastatic lesion significantly affect survival. Patients with residual tumor of 5 mm or less in diameter had a median survival of 40 months, compared with 18 months for those with residual disease between 5 and 15 mm and six months for those with a residual mass larger than 15 mm ($P<.001$). For patients whose tumors could be optimally cytoreduced, those without clinical ascites had a median survival of 32 months compared with 12 months for those with ascites ($P<.03$). For those whose largest metastatic disease was 10 cm or smaller before optimal cytoreduction, the median survival was 36 months compared with 12 months for those with metastatic disease larger than 10 cm ($P<.01$). The survival was independent of patient age, tumor grade, the type of chemotherapy and the diameter of the primary lesion.

In spite of these strong retrospective analyses, many physicians do not believe in the value of tumor cytoreduction in patients with epithelial ovarian malignancy. A randomized prospective study is necessary to address this issue, but until the results of such a study are available, we feel that, in view of the proved low morbidity associated with aggressive primary cytoreduction, it should be the standard of care for patients with advanced ovarian cancer.

In patients with no gross evidence of disease outside the pelvis (stages I and II), a thorough staging procedure is undertaken to rule out occult dissemination. A staging laparotomy includes doing an omentectomy, selective lymphadenectomy, multiple intraperitoneal biopsies and a peritoneal cytologic examination.

Operative procedures required for cytoreduction of ovarian cancer are not uniformly understood. Despite misconceptions to the contrary, tumor masses can usually be removed without being transected because lines of cleavage between tumor-bearing peritoneum and normal tissue are usually found. Omentectomy is carried out by ligating the gastroepiploic vessels along the greater curvature of the stomach, exposing the lesser sac and transverse mesocolon.[7] Although bowel or lower urinary tract resections are occasionally necessary, tumor implants can usually be removed

from the bowel or bladder serosa by sharp dissection.[9,10] Excision of all gross tumor in the pelvis is facilitated by a retroperitoneal dissection along the iliac vessels and ureters from the pelvic brim to the lower limit of tumor growth.

Radiation Therapy

The role of radiation therapy for patients with ovarian cancer is being redefined. Dembo and co-workers[11] prospectively evaluated the use of whole abdomen irradiation in patients, most of whom (86 percent) had disease confined to the pelvis (stages IB and II); they achieved a 78 percent five-year actuarial relapse-free survival. They used the so-called moving-strip technique for abdominopelvic irradiation and extended the upper limits of the field to 1 cm above the diaphragm. Their results were better than any previously reported, an improvement they attributed to adequate irradiation of the diaphragm, a frequent site of occult disease. Whole abdomen irradiation is now being more widely evaluated in the hope of more precisely defining the patient population most likely to benefit from this mode of therapy. For early stage disease that can be completely resected, radiocolloids such as radioactive phosphorus (^{32}P) and gold (^{198}Au) have been used and have been reported to augment survival in such patients.[12]

We have used whole abdomen irradiation as "second-line" treatment in some patients with incomplete responses to primary chemotherapy, and in whom there is little residual disease. Bone marrow intolerance is sometimes a problem, but we have been encouraged by the initial results in patients able to tolerate the therapy without significant treatment delays.

Second-Look Operations

Following a course of chemotherapy, typically consisting of 8 to 12 cycles, a second-look laparotomy is done if a patient is clinically free of disease. If any gross disease is present, an attempt is made to resect as much of it as possible before the institution of second-line therapy. If no gross tumor is present, a thorough inspection of all the intraabdominal viscera is made, multiple peritoneal washings are done for cytologic study and multiple biopsy specimens are taken from peritoneal surfaces and retroperitoneal lymph nodes. Recently it has become apparent that prolonged use of alkylating agents is associated with a significantly increased risk of acute nonlymphocytic leukemia developing; hence, prolonged therapy is unwise.[13] In about 30 percent to 40 percent of patients in clinical remission, findings will be negative on second-look laparotomies, thus permitting discontinuing their chemotherapy. About 75 percent of patients with negative findings on a second laparotomy will survive five years without clinical evidence of recurrence.[14]

It has also been suggested that laparoscopy (peritoneoscopy) may be useful in monitoring response to chemotherapy. Serial laparoscopies may be carried out on patients in clinical remission (for example, at four- to six-month intervals), thus allowing subclinical progression of disease to be detected at the earliest possible time so that alternative therapies may be instituted.[15]

At the time of a secondary operation for patients with ovarian cancer, either at "second look" or to assess clinical progression, the question arises as to whether or not persistent tumor should be resected. Based on a recent review of our clinical experience in 32 patients, we found optimal secondary resection of tumor was associated with a significantly longer median survival.[16] The feasibility of optimal resection, however, was only 38 percent, compared with 66 percent for patients who underwent primary tumor debulking. The median survival of patients who had an optimal secondary cytoreductive operation was 20 months compared with only five months for the nonoptimal group ($P<.01$). Patients who had clinically inapparent ascites fared much better than those with gross ascites (18 versus 5 months) ($P<.01$). Patients with smaller tumors (5 cm or less in maximum diameter) before resection had a median survival of 20 months, compared with only six months in those with larger tumors ($P<.01$). Patient age, tumor grade, the type of chemotherapy and the presence of bowel obstruction per se did not influence the subsequent survival. Thus, for patients who have incomplete responses to chemotherapy and have tumor discovered at second look, an attempt should be made to resect the residual disease. Furthermore, patients with clinical progression, if without ascites, may also benefit from tumor resection if feasible.

Prospects for the Future

With aggressive primary surgical treatment and multiagent chemotherapy, an increasing number of patients is being seen with complete clinical responses and minimal residual disease at second-look laparotomies. Our major research efforts are

now being directed toward the development of effective second-line therapies for this group of patients.

Intraperitoneal Chemotherapy

A major new development is the intraperitoneal administration of chemotherapy. Our group is studying the feasibility and toxicity of the intraperitoneal administration of cisplatin in women with persistent or recurrent carcinoma confined to the peritoneal cavity. Current data derived from studies with animals done at UCLA have shown that following intraperitoneal administration of cisplatin, drug concentrations in tissues lining the peritoneal cavity are 2½ to 8 times higher than following intravenous administration of the same dose of the drug.[17] Because ovarian cancer implants on peritoneal surfaces, intraperitoneal administration should result in maximal drug concentration in the tumor. The drug is administered through an indwelling intraperitoneal (Tenckhoff) catheter, and we have found this therapy to be well tolerated by patients. Because the drug does not remain in the peritoneal cavity for long, systemic absorption and toxicity are decreased.[18]

Intraperitoneal Immunotherapy

Immunotherapy has been most effective in animals when tumor burdens are small and immunologic agents can be brought into direct contact with tumor cells.[19] Hence, intraperitoneal immunotherapy might be expected to significantly prolong survival in ovarian cancer patients by eliminating the small number of tumor cells that remain following administration of chemotherapy.

Corynebacterium parvum has exerted antitumor activity in a variety of animals. From a recent review of other articles, *C parvum* appears to offer advantages over some other immunostimulants, particularly because of its effect on natural-killer lymphocyte and macrophage function, the stimulation of which seems important for tumor cell destruction in the peritoneal cavity.[19]

A collaborative phase I trial of intraperitoneally administered *C parvum* is under way at UCLA and the Sidney Farber Cancer Center in Boston. Thus far, 12 patients have received therapy and five have responded, three with complete surgical responses.

Hormone Receptors

The role of estrogen and progesterone receptors in neoplastic tissues has been extensively studied in breast cancer, but the technology has only recently been applied to the assessment of the female genital tract. In our laboratories, we have preliminary data that have suggested for the first time that levels of estrogen and progesterone receptors can be correlated with the histologic type and tumor grade of the ovarian carcinomas.[20] This implies that a more rational approach can be developed for the clinical use of antiestrogen and progestational agents for the treatment of advanced ovarian cancer.

Clonogenic Assay

The tumor colony, "clonogenic" assay, is now being used to determine the in vitro sensitivity to various chemotherapeutic agents before beginning therapy for ovarian cancer. The test helps to individualize the treatment, especially by excluding those drugs without apparent efficacy. If the test shows absence of in vitro sensitivity, the clinical response rate is less than 10 percent whereas positive sensitivities correlate with clinical responses in about 40 percent to 50 percent of patients.[21]

Monoclonal Antibodies

The pioneering work of Köhler and Milstein[22] has accomplished a potentially giant step in immunotherapy technology. Mouse myeloma cells were successfully fused with lymphocytes from the spleen of mice immunized with a particular antigen. The product was a hybrid myeloma cell, a so-called hybridoma. These new hybrid cells could express the lymphocyte's property of specific antibody production. Individual hybrid cells can be cloned and each clone can thus produce large quantities of identical antibody to a single antigenic determinant.

Monoclonal antibodies can be raised against antigenic determinants on human ovarian cell lines.[23] Furthermore, the method may potentially be applied to the serologic diagnosis, and the treatment of ovarian cancer. Research is currently being done to develop monoclonal antibodies in patients with ovarian cancer in an effort to establish a technique for early detection and monitoring of the disease. These antibodies may also prove to have some therapeutic value in ovarian cancer, particularly in patients with small residual disease.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Challenge Food Testing for Rheumatoid Arthritis

QUESTION:

Is it accepted medical practice to perform diagnostic evaluation of food allergy as a cause of rheumatoid arthritis?

If yes, is it accepted practice to hospitalize the patient for a 96-hour fast followed by reintroduction of foods into the diet one at a time to observe symptoms? Are other diagnostic methods accepted for evaluation of food allergy as a cause of rheumatoid arthritis?

OPINION:

In the opinion of the Advisory Panels on Allergy, Internal Medicine and Orthopedics, it is not accepted medical practice to perform diagnostic evaluation of food allergy as a cause of rheumatoid arthritis. There is no established scientific information or theoretical basis for considering food allergy as a cause or contributing factor to this disease.

Some panelists noted that the evaluation of food allergy in rheumatoid arthritis could be the subject of investigation under a well-planned research protocol. The use of a 96-hour fast in hospital, followed by reintroduction of foods, would be unnecessary for most investigators. Simple elimination diets on an outpatient basis and double-blind challenges are acceptable medical procedures to make the diagnosis of food allergy.